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Steady-state analyses of generic PBPK models for volatile organic chemical (VOC) exposure and risk assessment have been undertaken and applied for nearly two decades now.⁽¹⁻⁵⁾ Chiu and White’s paper on this subject adds little new to this earlier work. Their dismissive claim that “Similar analyses have been done for specific chemicals^(3,4) and for inhalation⁽⁵⁾” is misleading, because some of this earlier work did indeed focus on “generic” PBPK models generally applicable to VOC exposure by multiple routes. In particular, the earliest of these previous studies^(1,3,4) developed steady-state solutions for generic PBPK models including respiratory and 1-compartment oral routes of exposure, and further specified how to add injection and dermal exposure routes. Chiu and White included a 2-compartment oral pathway and a lung compartment in an otherwise identical generic PBPK model, but did not consider other exposure pathways such as dermal uptake. Each of the earlier studies^(1,3,4) first presented a steady-state solution to a generic, multiroute PBPK model, and only then applied the generic solution to a problem or illustration involving a specific compound—i.e., the same approach used later by Chiu and White. For example, my earlier study⁽³⁾ included a simple, intuitive expression for low-dose metabolized fraction f_m^* of any applied multiroute dose, allowing route-to-route extrapolation regardless of compound in low-dose contexts that typically are of interest in environmental VOC risk assessment. Section 2.2 of Chiu and White’s paper (“Generalization to Time-Varying Exposures”) concludes that, under conditions of virtually linear metabolism, PBPK system “solutions to steady-state exposures are directly applicable to intermittent exposures”—i.e., under such conditions, all steady-state system solutions (or output states) become valid when each dynamic input is replaced by its corresponding time-weighted average value. This conclusion, a well known axiom of linear systems theory, was stated explicitly to apply to f_m^* in my earlier study.⁽³⁾ A subsequent study⁽²⁾ addressed how generic steady-state PBPK solutions can be modified to estimate transient peak target-tissue concentrations at dynamic equilibrium, for dynamic exposure scenarios that involve exposure to a regular (e.g., daily) series of brief inputs by multiple pathways—an issue (not addressed by Chiu and White) that may be of importance for endpoints that have a cytotoxic mechanism of action.

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